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2-(HETERATOM-SUBSTITUTED)METHYL PENEMS:
II SULPHINYL AND SULPHONYL DERIVATIVES

Marco Alpegiani, Ettore Perrone, and Giovanni Franceschi
Farmitalia Carlo Erba S.p.A. - R & D, Infectious Diseases Dept.,
Via dei Gracchi, 35 - 20146 Milan, Italy

Abstract - Thermodynamic control of the endo-exo double bond equilibration in 2-(thio-
substituted)methyl penems allowed the synthesis of the sulphinyl and sulphonyl deriva-
tives, which proved to be potent antibacterial agents.

Recently\(^1\) we reported on the chemistry and biological activity of 2-thiomethyl penem derivatives I, pointing out that some incongruities of the microbiological results could be ascribed to their equilibrium to the isomeric thiomethylene penem structure II.

\[ \text{I} \quad n=0 \]
\[ \text{II} \quad n=1 \]
\[ \text{III} \quad n=2 \]

To complete the "sulphur series" of 2-CH\(_2\)X penems, we looked for substituents possessing an increased electron-withdrawing ability coupled with the intrinsic aptitude to stabilize the endo over the exo-
cyclic ene form. These requirements are fulfilled by the sulphinyl and sulphonylmethyl penems III, IV, which are the object of the present communication.

For the preparation of sulphoxide derivatives III a straightforward method was found in the regio-
selective oxidation of the easily accessible thiomethylene penems II. Accordingly, Bu\(_4\)NF-mediated desilylation of the penem 4b\(^1\) afforded the penem 6, whose treatment with 1 eq MCPBA (CH\(_2\)Cl\(_2\), -40°C) followed by workup with aqueous sodium metabisulphite led to isolation of penem 9a as a mixture of sulphoxide epimers in virtually quantitative yield (Scheme 1). Regioselectivity in the oxidation is accounted for by the preferential attack of MCPBA to the sterically less hindered sulphur atom, while the exo-end0 double bond isomerization results from thermodynamic factors favouring allyl sulphones over the isomeric vinyl sulphones\(^2\). In fact, in the absence of the peripheral sulphur, oxidation of methylene penems uneventfully occurs on the nucleus with preservation of the exo structure\(^3\). An intra-annular counterpart of this double bond shift is the well-known conversion of \(\Delta^2\) cephems into \(\Delta^3\) cephem-1-oxides.

Removal of the pNB protecting groups from 9a by catalytic hydrogenation proved unexpectedly diffi-
SCHEME 1

1. \( R^1 = \text{CO}_2 \text{pNB}, \quad R^2 = \text{pNB} \\
2. \( R^1 = \text{SiMe}_2 \text{Bu}^t, \quad R^2 = \text{allyl} \\

\begin{align*}
\text{OR}^1 & \quad \text{HS} \quad \text{OR} \\
\text{CO}_2 R^2 & \quad \text{OR}^1 \\
\end{align*}

3. \( a \quad R = \text{SiMe}_2 \text{Bu}^t \\
   b \quad R = \text{SiPh}_2 \text{Bu}^t \\

4. \( R^1 = \text{CO}_2 \text{pNB}, \quad R^2 = \text{pNB} \\
5. \( R^1 = \text{SiMe}_2 \text{Bu}^t, \quad R^2 = \text{allyl} \\

6. \( R^1 = \text{CO}_2 \text{pNB}, \quad R^2 = \text{pNB} \\
7. \( R^1 = \text{SiMe}_2 \text{Bu}^t, \quad R^2 = \text{allyl} \\

\begin{align*}
\text{OSiMe}_2 \text{Bu}^t & \\
\text{CO}_2 R^2 & \\
\end{align*}

8. \( R^3 = \text{OH} \\
   a \quad R^3 = \text{OH} \\
   b \quad R^3 = \text{OCONH}_2 \\
   c \quad R^3 = \text{NO} \\
   d \quad R^3 = \text{NO} \\
   e \quad R^3 = \text{NO} \\

9. \( R^1 = \text{CO}_2 \text{pNB}, \quad R^2 = \text{pNB} \\
10. \( R^1 = \text{SiMe}_2 \text{Bu}^t, \quad R^2 = \text{allyl} \\
11. \( R^1 = \text{H}, \quad R^2 = \text{allyl} \\

\begin{align*}
\text{OH} & \\
\text{CO}_2 \text{Na} & \\
\end{align*}

12. \( a,b \quad \text{OH} \quad \text{OH} \\
12. \( c,d,e \quad \text{OH} \quad \text{OH} \\

- 50 -
cult. To overcome this problem, the differently protected methylene penam was preferred to the key intermediate for the synthesis of 12a. Reaction of the alkyl thiol 3a (3b) with hydroxymethyl penam under a slightly modified Mitsunobu-Volante procedure (slow addition of a preformed PPh3-DiAD complex to a mixture of 2 and 3 in refluxing dichloromethane) furnished a 1:1 penem-penam mixture 5a (5b) in 73% (81%) yield. Selective cleavage of the primary silyl ether in 5a and 5b (1.5 eq Bu4NF·3H2O, 5 eq HOAc, THF, few hours) occurred as expected with concomitant double bond isomerization, affording 7 in satisfactory yield (68-75%). When 7 was subjected to MCPBA oxidation, penem 10a (1:1 mixture of epimeric sulfoxides) was exclusively obtained. In accordance with well-established procedures, 10a underwent desilylation and deblocking of the allyl group to furnish the sodium salt 12a in 65% yield.

The strong antibacterial activity of 12a (Table III) prompted us to synthesize some analogues bearing functionalities whose beneficial effect had been previously observed in the penem area. Preparation of the carbamate 12b entailed condensation of the alcohol 10a with trichloroacetyl isocyanate (CH2Cl2, 1 minute, quant.) followed by simultaneous removal of the secondary silyl ether and trichloroacetyl group (Bu4NF·3H2O, HOAc-THF, overnight) and final unmasking of the allyl ester (38% overall). A quaternary ammonium group was conveniently introduced at an earlier stage. Thus, reaction of the penam carbinol 7, insitu activated as its triflate (trifluoromethanesulphonanhydride, 2.5 eq. pyridine, CH2Cl2, −70°C → 0°C), with an excess of the selected tertiary nitrogen nucleophile occurred with partial exo-endo double bond isomerization providing 10c—e, which underwent mild oxidation (1 eq. MCPBA, CH2Cl2, −70°C → 30°C, 15 min) to the epimeric sulfoxides 10c—e, uncontaminated by any penam isomer. Subsequent routine desilylation and catalytic transallylation with excess acetic acid (Pd(PPh3)4, PPh3, CH3CN-CH2Cl2, 30 min., 12% overall from the alcohol) yielded the zwitterions 12c—e. The carbamate 12b exhibited excellent antimicrobial activity, superior to the hydroxy analog 12a and to the reference compound FCE 22107, while an adverse effect was associated with the introduction of quaternary ammonium groups (entries 12c—e, Table III).

Table I - Spectral data of key intermediates

<table>
<thead>
<tr>
<th>Compd.</th>
<th>ν (max, cm⁻¹)</th>
<th>¹H nmr (δ, ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9a</td>
<td>1795,1745,1710</td>
<td>2.96(2H,m),3.99(1H,dd,J=1.8 and 7.5Hz),4.05(2H,m),4.01,4.06,4.56,4.61(2H, each d,J=13.3Hz),5.67(1H,d,J=1.8Hz)</td>
</tr>
<tr>
<td>10a</td>
<td>1790,1700</td>
<td>3.0-3.2(2H,m),3.83(1H,dd,J=1.7 and 4.1Hz),4.1-4.3(2H,m),4.11,4.26,4.64,4.74(2H, each d,J=13.3Hz),5.72(1H,d,J=1.7Hz)</td>
</tr>
<tr>
<td>14</td>
<td>3420,1425,1120,1010,990,700</td>
<td>(DMSO-d6)1.00(9H,s),2.29 and 3.88(each 2H,t,J=7.0Hz),7.25-7.78(10H,m)</td>
</tr>
<tr>
<td>15c</td>
<td>3550,1790,1700 (KBr)</td>
<td>2.61(1H,br,s),3.3-3.4(2H,m),3.79(1H,dd,J=1.7 and 4.0Hz),4.13(2H,m),4.47 and 4.93(2H, each d,J=14.4Hz),5.69(1H,d,J=1.7Hz)</td>
</tr>
</tbody>
</table>

1 In CDCl3 unless otherwise stated. 2 In DMSO-d6 unless otherwise stated. Signals due to C6 side chain and to protecting groups have been omitted.
Table II - Spectral data of 2-sulphinyl and 2-sulphonylmethylpenem-3-carboxylic acids (sodium or internal salts)

<table>
<thead>
<tr>
<th>Compound</th>
<th>ir(KBr) v max (cm⁻¹)</th>
<th>uv (H₂O) λ max (nm)</th>
<th>1H nmr (D₂O unless otherwise stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>1765,1600</td>
<td>258,316</td>
<td>(DMSO-d₆) 1.12(3H,d,J=1.5 and 6.9Hz), 3.49 (1H,dd,J=3.7 and 5.7Hz), 3.73(2H,m), 4.07,4.32(4H,br s,exch D₂O), 5.05 (1H,br s,exch D₂O), 5.11(1H,br s,exch D₂O), 5.42-5.54(1H, each d,J=1.5Hz)</td>
</tr>
<tr>
<td>12b</td>
<td>1760,1715,1605</td>
<td>255(ε=4185), 315(ε=6004)</td>
<td>(DMSO-d₆) 1.13(3H,d,J=6.3Hz), 2.8-3.2(2H,m), 3.50 (1H,dd,J=1.5 and 6.9Hz), 3.87(1H,m), 4.07,4.32(4H,br s,exch D₂O), 5.05 (1H,br s,exch D₂O), 5.11(1H,br s,exch D₂O), 5.42-5.54(1H, each d,J=1.5Hz)</td>
</tr>
<tr>
<td>12c</td>
<td>1760,1620-1590</td>
<td>259,316</td>
<td>1.30(3H,d,J=6.3Hz), 3.6-3.7(2H,m), 3.95(1H,dd,J=1.7 and 5.9Hz), 4.25(1H,dq,J=5.9 and 6.3Hz), 4.33,4.72(2H, each d,J=13.6Hz), 5.19(2H,m), 5.69 (1H,d,J=1.7Hz), 5.14(2H,dd,J=5.6 and 7.0Hz), 8.63 (1H,t,J=7.0Hz), 8.99(2H,d,J=5.6Hz)</td>
</tr>
<tr>
<td>12d</td>
<td>1765,1605</td>
<td>259,317</td>
<td>1.29(3H,d,J=6.4Hz), 2.26(4H,m), 3.13(3H,s), 3.60 (4H,m), 3.5-4.0(4H,m), 3.99(1H,dd,J=1.5 and 6.0Hz)</td>
</tr>
<tr>
<td>12e</td>
<td>1770,1605</td>
<td>261,316</td>
<td>1.30(3H,d,J=6.4Hz), 3.29(3H,s), 3.60(4H,m), 3.5-4.0 (4H,m), 4.09(4H,m), 4.26(1H,dq,J=5.9 and 6.4Hz), 4.37,4.74(2H, each d,J=13.4Hz), 5.73,5.74(1H,each d,J=1.5Hz)</td>
</tr>
<tr>
<td>12f</td>
<td>1765,1610</td>
<td>258,314</td>
<td>1.30(3H,d,J=6.4Hz), 3.16(3H,s), 3.98(1H,dd,J=1.5 and 5.7Hz), 4.26(2H,m), 4.69,509(2H, each d,J=14.2 Hz), 5.73(1H,d,J=1.5Hz)</td>
</tr>
<tr>
<td>12g</td>
<td>1785,1600</td>
<td>256(ε=5212), 314(ε=6900)</td>
<td>1.30(3H,d,J=6.3Hz), 3.54(2H,t,J=5.6Hz), 3.98(1H,dd, J=1.6 and 6.0Hz), 4.07(2H,t,J=5.6Hz), 4.26(1H,dq,J=6.0 and 6.3Hz), 4.70,5.13(2H,each d,J=14.1Hz), 5.73 (1H,d,J=1.6Hz)</td>
</tr>
<tr>
<td>12h</td>
<td>1760,1715,1605</td>
<td>259,313</td>
<td>1.32(3H,d,J=6.4Hz), 3.73(2H,t,J=5.2Hz), 4.01(1H,dd, J=1.6 and 6.0Hz), 4.28(1H,dq,J=6.0 and 6.4Hz), 4.52 (2H,t,J=5.2Hz), 4.73,5.24(2H, each d,J=14.2Hz), 5.75(1H,d,J=1.6Hz)</td>
</tr>
<tr>
<td>12i</td>
<td>1785,1605</td>
<td>313(ε=6275)</td>
<td>1.34(3H,d,J=6.4Hz), 3.7-3.9(4H,m), 3.97(1H,dd,J=1.6 and 6.0Hz), 4.04(3H,m), 4.27(1H,dq,J=6.0 and 6.4Hz), 4.83,5.13(2H, each d,J=14.6Hz), 5.74(1H,d,J=1.6Hz)</td>
</tr>
</tbody>
</table>

At this point we turned our attention to the synthesis of sulphonylmethylpenemens IV, which offered further reasons for interest. Not only thermodynamic control favours allyl sulphones over vinyl sulphones, thereby inhibiting the penem → penem isomerization as for the corresponding sulphotides, but the sulphonyl group compared to the sulphinyl group enhances the β-lactam reactivity by exerting a stronger electron-withdrawing power, and avoids handling with epimeric mixtures. In Scheme 2 a practical synthetic route to sulphonylmethyl penemens is outlined, involving conversion of 2 into the chloromethyl penem 3, followed by displacement with the appropriate alkanesulphinate anion.
Thus, treatment of \(13\) with sodium methanesulphonate and with sodium t-butyldiphenylsilyloxyethane-
sulphonate \(14\) \((\text{DMF, 3h, 50-70\%})\) afforded the crystalline \(^{13}\) sulphones \(15a\) and \(15b\), respectively. Stepwise removal of protecting groups from \(15a\) uneventfully gave \(16a\) and \(17a\) \((48\%\) over the two steps). Cleaveage of the primary silyl ether on the fully protected penem \(15b\) could be achieved selectively \((1.2\, \text{eq.}, \text{Bu}_4\text{NF}, \text{THF}, \text{HOAc}, \text{6h})\) furnishing the carbinoi \(15c\) \((73\%)\), together with appreciable amounts of the diol \(16c\) \((\sim 20\%)\) after prolonged exposure \((24\, \text{h})\) to excess \((6\, \text{eq.})\) reagent. Conventional Pd-mediated deallylation gave the sodium salt \(17c\). The preparation of the carbamoyl derivatives \(11d\) from the alcohol \(15c\) paralleled the route followed in the sulfoxide series \((10a \rightarrow 12b)\). However, \(15c\) failed to behave like its analogue \(10a\) when treated with triflic anhydride /N-methylpyrrolidine \((\text{CH}_2\text{Cl}_2, -70^\circ\text{C} \rightarrow 0^\circ\text{C})\), the main isolated product being the vinyl sulphone \(15f\) \((30\%\) yield). In this case the leaving ability of the trflate and quaternary ammonium groups, associated with the acidity of the \(\alpha\)-sulphonyl protons, accounts for the occurrence of a competitive elimination reaction. Activation of the alcohol \(15c\) under Mitsunobu-Volante conditions \(^{5}\) \((\text{preformed TP/DEAD complex, THF, 1 min.})\) in the presence of 5-mercapto-1-methyl-1,2,3,4-tetrazole led to the formation of the correspondent heterocycl thiester \(15a\) in 90\% yield, the remainder being the elimination product \(15f\). Finally \(15a\) was converted into the sodium salt \(17a\) \((35\%\) overall) by following the usual deprotection protocol.

**Scheme 2**

![Scheme 2](image)
With the exception of 17e, all the sulphonylmethyl penems showed a quite remarkable level of in vitro antimicrobial activity, comparable to that of their analogues in the sulphoxide series (Table III). The minimal inhibitory concentration (MIC) values exhibited by the structurally related carbamates 17d, 12b and 18, only differing in the oxidation state of the extranuclear sulphur atom are worth noticing. In line with our original working hypothesis, an improvement in antibiotic performance was observed on changing from the thiaether representative 18 to the oxidated analogues, but the better profile exhibited by 12b in comparison with 17d could not be reduced in terms of straightforward structure-activity relationship.

![Diagram](image)

**Table III - In vitro antibacterial activity\(^1,2\) of penems**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>12a</td>
<td>0.045</td>
<td>0.005</td>
<td>0.78</td>
<td>1.56</td>
<td>0.78</td>
<td>0.78</td>
<td>1.56</td>
</tr>
<tr>
<td>12b</td>
<td>0.045</td>
<td>0.011</td>
<td>0.19</td>
<td>0.39</td>
<td>0.78</td>
<td>0.39</td>
<td>0.78</td>
</tr>
<tr>
<td>12c</td>
<td>0.09</td>
<td>------</td>
<td>6.25</td>
<td>3.12</td>
<td>3.12</td>
<td>6.25</td>
<td>6.25</td>
</tr>
<tr>
<td>12d</td>
<td>0.19</td>
<td>------</td>
<td>6.25</td>
<td>6.25</td>
<td>6.25</td>
<td>6.25</td>
<td>25</td>
</tr>
<tr>
<td>12e</td>
<td>0.39</td>
<td>------</td>
<td>6.25</td>
<td>6.25</td>
<td>6.25</td>
<td>6.25</td>
<td>25</td>
</tr>
<tr>
<td>17a</td>
<td>0.19</td>
<td>0.045</td>
<td>0.39</td>
<td>0.78</td>
<td>0.39</td>
<td>0.19</td>
<td>1.56</td>
</tr>
<tr>
<td>17c</td>
<td>0.09</td>
<td>0.045</td>
<td>0.78</td>
<td>1.56</td>
<td>0.78</td>
<td>0.78</td>
<td>1.56</td>
</tr>
<tr>
<td>17d</td>
<td>0.09</td>
<td>0.022</td>
<td>0.39</td>
<td>1.56</td>
<td>1.56</td>
<td>0.39</td>
<td>0.78</td>
</tr>
<tr>
<td>17e</td>
<td>0.09</td>
<td>0.022</td>
<td>3.12</td>
<td>3.12</td>
<td>12.5</td>
<td>6.25</td>
<td>3.12</td>
</tr>
<tr>
<td>PCE 22101</td>
<td>0.045</td>
<td>0.011</td>
<td>6.25</td>
<td>6.25</td>
<td>25</td>
<td>12.5</td>
<td>6.25</td>
</tr>
</tbody>
</table>

1) Minimal inhibitory concentrations (MICs, \(\mu g/ml\)) were determined by the standard two-fold agar dilution method in Bacto Antibiotic Medium 1 (Difco).
2) Organisms included in this Table are: S.a., Staphylococcus aureus Smith; S.p., Streptococcus pyogenes ATCC 12384; E.c., Escherichia coli B; E.c.\(^+\), E. coli B \(\beta\)-lactamase producer; E.cl.\(^+\), Klebsiella pneumoniae P99 \(\beta\)-lactamase producer; K.a., Klebsiella aerogenes 1522 E; P.m., Proteus morganii ATCC 25830.

ACKNOWLEDGMENTS

We thank Giuseppe Meinardi, Daniela Jabes and Costantino Della Bruna for the in vitro antibacterial activity data.
REFERENCES AND NOTES

9. The penem/penem ratio ranged from approximately 3:1 to 4:1, depending on the nature of the nitrogen nucleophile.
10. As detected by $^1$H NMR (200 MHz) spectroscopy.
12. Compound 14 was obtained from the corresponding mercaptan by exploiting the Michael adduct with ethyl acrylate as an oxidation blocker (81% overall):

\[
\text{BuPh}_2\text{SiOCH}_2\text{CH}_2\text{SH} + \text{NaH} \rightarrow \text{BuPh}_2\text{SiOCH}_2\text{CH}_2\text{SOCH}_2\text{COEt} + \text{Et}_2\text{SiOCH}_2\text{CH}_2\text{SH} 
\]

13. Melting points of the crystalline sulphone intermediates are as follows: 15a, 65°C; 15b, 144-146°C; 15c, 120-122°C; 16a, 118-120°C.

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